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ORIGINAL ARTICLE

Facile and new convenient route for synthesis of some C_2-symmetric bidentate phosphine ligands derived from D-mannitol

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Abstract The preparation of two novel C_2 symmetric bidentate phosphine ligands derived from cheap and available *D*-mannitol has been reported. These new ligands accompanied by unprecedented one-pot reaction for the regioselective reductive opening of 1,3:4,6-di-*O*-benzylidene-*D*-mannitol have been achieved. All reported compounds are fully characterized by standard analytical methods including the measurement of optical activities.

1. Introduction

The search for new ligands for homogeneous catalysis is a field of continuing interest. Huge efforts have been devoted to the development of highly efficient catalysts using ligands containing P,P, P,N and N,N modified with transition metals such as Ti, Pd, Rh and Ru (Desimoni et al., 2006; Jacobsen et al., 1999; Ojima, 2000; Schill and Meijere, 2007; Fang et al., 2003; Ngo and Lin, 2005; Aikawa et al., 2010; Ohshima et al., 2011; Roering et al., 2010). Asymmetric hydrogenation catalyzed by transition-metal is one of the most powerful methods for the synthesis of optically active compounds, and the design of new phosphorus chiral ligands plays a central role in this area. Although excellent enantioselectivities have been obtained by using such chiral diphosphine ligands, only few ligands have found broad applications in various types of asymmetric hydrogenation reactions (Claver et al., 2008). Carbohydrates are naturally enantiomeric pure compounds i.e. chiral pole, which have interesting stereochemical diversity. Apart from their biological role, they are important chiral auxiliaries for enantioselective organic syntheses. The carbohydrate metal interactions are of interest in such enantioselective syntheses (Holz et al., 1998), because homogeneous catalysis is one of the most important approaches for preparing enantiomeric pure compounds, carbohydrate derivatives have been found to be increasingly used as chiral ligands in the last decades (Holz et al., 1998; Gual et al., 2011). Bidentate ligands, in particular diphosphine one, have been considered the best ligands for transition metal asymmetric catalysis (Diéguez et al., 2004; Castillón et al., 2005) With the introduction of Kagan's DIOP, the first chiral diphosphine ligand (Pfaltz and Drury, 2004), the research on ligands for asymmetric catalysis focused on bidentate ligands. Knowles et al.

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showed that DIPAMP as chelate diphosphine ligand is superior to the corresponding monodentate species in rhodium catalyzed hydrogenation reactions of various types of substituted alkenes (Burk and Bienewald, 1998; Jacobsen et al., 1999). The uses of BINAP and DIPHOS ligands have also led to an extremely high enantiomeric excess (Burk and Bienewald, 1998; Jacobsen et al., 1999). In this work, we report on the synthesis of C_2 symmetric bidentate phosphine ligand. We have demonstrated a facile and direct synthesis of diphosphine ligands having acetal and ketal moieties, derived from *D*-mannitol. We also succeeded in developing an unprecedented one-pot reaction for the regioselective reductive opening of 1,3:4,6-di-*O*-benzylidene-*D*-mannitol.

2. Experimental

2.1. General

All the moisture and air sensitive reactions were carried out under an inert atmosphere using an argon filled glove box and standard Schlenk-line techniques. All the chemicals were purchased from Aldrich, Sigma–Aldrich and Fluka etc. and were used without further purification, unless otherwise stated. Pyridine, Et_3N and were distilled from fresh KOH. Diethyl ether and THF were distilled using Na/benzophenone. Hexane, heptanes and pentane were distilled using Na wires and benzophenone. $CHCl_3$, CH_2Cl_2 and DMF were dried from CaH_2. Flash column chromatography (FCC): silica gel (SiO_2; 100–200 mesh). All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR spectra were measured as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{31}P NMR were run in deuterated dimethylsulfoxide (DMSO-d_6 or $CDCl_3$). Chemical shifts (δ) are referred in terms of ppm and *J*-coupling constants are given in Hz. Mass spectra were recorded on a Jeol-JMS-600H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer; CHN mode. Optical rotations were measured on a Polarimeter, polax-2L.

2.1.1. General procedure for the preparation of Ketal protection (GP1)

Concentrated H_2SO_4 (0.7 equiv.) was added to a solution of *D*-mannitol (0.5 mol) and aldehyde derivatives (1.0 mol) in DMF (300 ml). The mixture was left at room temperature for 3 days. The reaction mixture was then poured into ice-water (3 l) containing potassium carbonate (30 g) and light petroleum (b. p. 60–80°; 500 ml). The mixture was stirred vigorously and a white solid was obtained as the ice melted. The solid was then filtered off, washed with light petroleum (b. p. 60–80°), and extracted with boiling $CHCl_3$ (2 × 200 ml). The residue was recrystallized from methanol to give the desired product.

*2.1.1.1. 1,3:4,6-di-O-benzylidene-D-mannitol (**1a**).* According to GP1, **1a** was obtained from reaction of *D*-mannitol (50 g, 0.27 mol) and benzaldehyde (62.5 g, 60 ml, 0.58 mol,) as a white solid (82.6 g, 0.23 mol, 84%), *m. p.* 192–193°; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45–7.43 and 7.39–7.34 (5H, *m*, Ph), 5.52 (1H, *s*, PhCH), 4.18 (1H, *q*, *J* = 10.2 Hz, OCH_2), 3.94 (1H, *d*, *J* = 8.8 Hz, OCH), 3.83 (1H, *m*, CH-OH), 3.58 (1H, *t*, *J* = 11 Hz, OCH_2), 3.36 (1H, *s*, OH). All other analytical data were in accordance with the literature (Sureshkumar et al., 2006).

*2.1.1.2. 1,3:4,6-di-O-tolylidene-D-mannitol (**1b**).* According to GP1, **1b** was obtained from *D*-mannitol (10 g, 0.05 mol) and tolualdehyde (16.91 g, 16.24 mL, 0.1 mol) as a white solid (82.6 g, 0.23 mol, 79%), *m. p.* 230°; $[\alpha]_D^{24} = -38°$ (*c* = 1.0 g/dL, *DMSO*); IR (KBr, cm^{-1}): *v* = 3485, 1617, 1368; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.31 (2H, *d*, *J* = 8.0 Hz, Ph), 7.17–7.15 (2H, *d*, *J* = 8.0 Hz, Ph), 5.46 (1H, *s*, PhCH), 4.38 (1H, *q*, *J* = 10.2 Hz, OCH_2), 4.34 (1H, *m*, CH-OH), 4.15 (1H, *d*, *J* = 8.8 Hz, OCH), 3.65 (1H, *t*, *J* = 10.2 Hz, OCH_2), 2.99 (1H, *s*, O*H*), 2.35 (3H, *s*, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 134.2, 129.1, 125.8, 101.74, 80.6, 70., 61.7, 21.3; MS (*m*/*z*): 385.3 (M^+), 10%; Anal. for $C_{22}H_{26}O_6$ calcd; C, 68.38; H, 6.78. Found: C, 68.27; H, 6.69.

*2.1.1.3. 1,3:4,6-di-O-(4-methoxybenzylidene)-D-mannitol (**1c**).* According to GP1, **1c** was obtained from reaction of *D*-mannitol (10 g, 0.05 mol) and *p*-methoxybenzaldehyde (15.00 g, 13.35 ml, 0.1 mol) as a white solid (39.58 g, 0.09 mol, 86%), *m. p.* 218°; IR (KBr, cm^{-1}): *v* = 3451, 1612, 1369; $[\alpha]_D^{24} = -58°$ (*c* = 1.0 g/dL, *DMSO*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (2H, d, *J* = 8.8 Hz, Ph), 6.89 (2H, d, *J* = 8.8 Hz, Ph), 5.44 (1H, *s*, PhCH), 4.36 (1H, *q*, OCH_2), 4.28 (1H, *m*, CH-OH), 4.11 (1H, d, *J* = 8.8 Hz, OCH), 3.80 (3H, *s*, OCH_3), 3.61 (1H, *t*, *J* = 10.2 Hz, OCH_2), 3.00 (1H, *s*, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 128.2, 113.9, 101.5, 80.5, 70.6, 61.6, 55.3; MS (*m*/*z*): 419.5 $(M+1)^+$, 17%; Anal. for $C_{22}H_{26}O_8$; calcd: C, 63.15; H, 6.26. Found: C, 63.20; H, 6.30.

*2.1.1.4. 1,3:4,6-di-O-(2,4-dichlorobenzylidene)-D-mannitol (**1d**).* According to GP1, **1d** was obtained from reaction of *D*-mannitol (10 g, 0.05 mol) and benzaldehyde (19.25 g, 0.1 mol) as a white solid (54.05 g, 0.10 mol, 80%), *m. p.* 158°; $[\alpha]_D^{24} = -48°$ (*c* = 1.0 g/dL, *DMSO*); IR (KBr, cm^{-1}): *v* = 3363, 1593, 1377; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (1H, *s*, Ph), 7.27–7.17 (2H, *dd*, *J* = 9.5 Hz, 8.0 Hz Ph), 6.13 (1H, *s*, PhCH), 4.33 (1H, *q*, OCH_2), 4.29 (1H, *m*, CH-OH), 4.17 (1H, *d*, *J* = 8.8 Hz, OCH), 3.85 (1H, *t*, *J* = 10.2 Hz, OCH_2), 2.94 (1H, *s*, OH)ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1 (C−), 134.0, 129.6, 128.0, 99.9, 76.4, 71.0, 68.3; MS (*m*/*z*): 419.5 $(M+)^+$, 17%; Anal. for $C_{20}H_{18}Cl_4O_6$ calcd; C, 48.41; H, 3.66. Found: C, 48.50; H, 3.52.

*2.1.1.5. 1,2:5,6-di-O-isopropylidene-D-mannitol (**6**).* This compound was prepared according to procedure described by Al Majid et al. (2010).

2.1.2. General procedure for the preparation of bismesylate derivatives (GP2)

To a solution of protected DIOL **1a–d** (19.08 mmol) in dry pyridine (25 ml) was stirred at 0° under N_2. After stirring for 10 min, CH_3SO_2Cl (45.5 mmol) was then added *via* drop wise at 0 °C over a period of 15 min and the reaction mixture was then allowed to stir at 0 °C for 1.5 h. The reaction mixture was kept in the fridge over night, water (3 ml) was then added, extracted with chloroform (3 × 50 ml) and the organic phase washed with 10% HCl (1 × 100 ml), H_2O (1 × 100 ml), 5%

Na_2CO_3 (1 × 100 ml), brine (1 × 100 ml), dried over $MgSO_4$, filtered off and evaporated to yield a yellow oily crude product which upon dissolved in cold Et_2O and evaporated gave the desired bismesylate derivatives (Al Majid et al., 2010).

2.1.2.1. 3,4-Bis-o-mesyl-1,2:5,6-di-O-isopropylidene-D-mannitol (7). According to **GP2**, the bismesylate **7** was obtained from reaction of **6** (5.0 g, 19.08 mmol), and CH_3SO_2Cl (3.5 ml, 45.5 mmol, in freshly-distilled pyridine (25 ml) as a colorless crystals (7.0 g, 16.72 mmol, 88% yield), *m. p.* 105°; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (1H, *d*, *J* = 7.4 Hz), 4.25 (1H, *q*, OCH), 4.16 (2H, *d*, *J* = 5.1 Hz, CH_2), 3.17 (3H, *s*, SO_2CH_3), 1.41 (3H, *s*, CH_3), 1.34 (3H, *s*, CH_3). All other analytical data were in accordance with the literature [16].

*2.1.2.2. 2,5-Bis-o-mesyl-1,3:4,6-di-O-benzylidene-D-mannitol (**2a**)*. According to GP2, **2a** was obtained from **1a** (3.0 g, 8.37 mmol) in dry pyridine (10 ml) and CH_3SO_2Cl (1.43 ml, 2.11 g, 18.41 mmol) as a white solid (4.2 g, 8.16 mmol, 97% yield), *m. p.* 205°; ^{1}H NMR (400 MHz, $CDCl_3$, 21°): δ = 7.50–7.35 (5H, m, Ph), 5.52 (1H, s, PhCH), 5.06 (1H, m, MsOCH), 4.58 (1H, *q*, OCH_2), 4.16 (1H, *d*, *J* = 8.8 Hz, OCH), 3.88 (1H, *t*, *J* = 10.2 Hz, OCH_2). All other analytical data were in accordance with the literature [30].

*2.1.2.3. 2,5-Bis-o-mesyl-1,3:4,6-di-O-tolylidene-D-mannitol (**2b**)*. According to GP2, **2b** was obtained from reaction of **1b** (1.0 g, 2.58 mmol) dissolved in dry pyridine (5 ml) with CH_3SO_2Cl (0.44 ml, 0.65 g, 5.6 mmol) as a yellowish solid (1.65 g, 3.04 mmol, 84.4% yield) *m. p.* 90°; $[\alpha]_D^{24} = -10°$ (*c* = 1.0 g/dL, *$CHCl_3$*); IR (KBr, cm^{-1}): *v* = 1604, 1342; ^{1}H NMR (400 MHz, $CDCl_3$): 7.37–7.35 (2H, *d*, *J* = 8.0 Hz, Ph), 7.18–7.16 (2H, *d*, *J* = 8.0 Hz, Ph), 5.47 (1H, *s*, PhCH), 5.02 (1H, *m*, SO_3CH), 4.56 (1H, *q*, OCH_2), 4.13 (1H, *d*, *J* = 8.8 Hz, OCH), 3.84 (1H, t, *J* = 10.2 Hz, OCH_2), 3.00 (3H, *s*, SO_2CH_3), 2.35 (3H, *s*, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 133.6, 129.0, 126.2, 101.9, 76.7, 75.1, 66.5, 38.0, 21.3; MS (*m*/*z*): 542.5 (M^+), 17%; Anal. for $C_{24}H_{30}O_{10}S_2$ calcd; C, 53.12; H, 5.57. Found: C, 53.10; H, 5.59.

*2.1.2.4. 2,5-Bis-o-mesyl-1,3:4,6-di-O-(4-methoxybenzylidene)-D-mannitol (**2c**)*. According to GP2, **2c** was obtained from **1c** (2.0 g, 4.8 mmol) in dry pyridine (10 ml) and CH_3SO_2Cl (0.83 ml, 1.22 g, 10.56 mmol) as an oily product (2.3 g, 4.0 mmol, 84% yield); $[\alpha]_D^{24} = -60°$ (*c* = 1.0 g/dL, *$CHCl_3$*); IR (KBr, cm^{-1}): *v* = 1592; ^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (2H, *d*, *J* = 8.0 Hz, Ph), 7.00 (2H, *d*, *J* = 8.0 Hz, Ph), 5.52 (1H, *s*, PhCH), 5.02 (1H, *m*, SO_2CH), 4.30 (1H, *q*, OCH_2), 4.13 (1H, *d*, *J* = 8.8 Hz, OCH), 3.87 (3H, *s*, OCH_3), 3.78 (1H, *t*, *J* = 10.2 Hz, OCH_2), 3.01 (3H, *s*, SO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 132.1, 127.6, 114.4, 113.7, 76.8, 66.3, 55.6), 37.6; MS (*m*/*z*): 575 (M^+), 22%; Anal. for $C_{24}H_{30}O_{12}S_2$ calcd; C, 50.16; H, 5.26. Found: C, 50.05; H, 5.20.

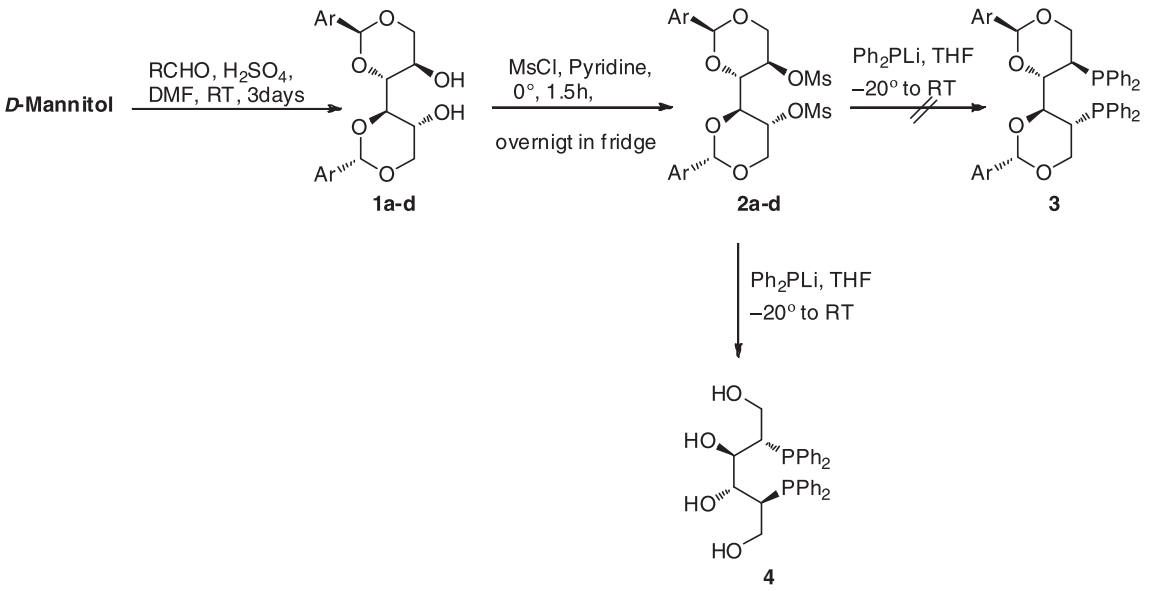
*2.1.2.5. 2,5-Bis-o-mesyl-1,3:4,6-di-O-(2,4-dichlorobenzylidene)-D-mannitol (**2d**)*. According to GP2, **2d** was obtained from **1d** (2.0 g, 4.03 mmol) in dry pyridine (10 ml) and CH_3SO_2Cl (0.7 ml, 1.02 g, 8.86 mmol) as white sponge 2.5 g, 3.83 mmol, 95% yield); *m. p.* 62°; $[\alpha]_D^{24} = +75°$ (*c* = 1.0 g/dL, *$CHCl_3$*); IR (KBr, cm^{-1}): *v* = 1592, 1360; ^{1}H NMR (400 MHz, $CDCl_3$, 21°): δ = 7.40 (1H, *s*, Ph), 7.28–7.18 (2H, *dd*, *J* = 9.5 Hz, 8.0 Hz, Ph), 6.13 (1H, *s*, PhCH), 4.45 (1H, *q*, OCH_2), 4.27 (1H, *m*, CH-OH), 4.14 (1H, *d*, *J* = 8.8 Hz, OCH), 3.24 (1H, *t*, *J* = 10.2 Hz, OCH_2), 2.99 (3H, *s*, SO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 134.0, 129.6, 128.0, 101.0, 76.7, 74.1, 68.3, and 38.9; MS (*m*/*z*): 652.1 (M^+), 17%; Anal. for $C_{22}H_{22}Cl_4O_{10}S_2$. calcd; C, 40.51; H, 3.40. Found: C, 40.55; H, 3.46.

*2.1.2.6. 2,5-Bis-o-diphenylphosphino-D-mannitol (**4**)*. To a solution of mesylate derivatives **2** (1.0 g, 1.74 mmol) in THF (10 .0 ml) were added Ph_2PLi (0.5 M) (10.44 ml, 5.22 mmol) at −20° under an atmosphere of argon. The reaction was then warmed to RT over night, quenched with water (50 ml), extracted with EtOAc (3 × 50 ml), washed with brine, and dried over $MgSO_4$. The solvent was evaporated and subsequently the residue was purified by column chromatography using a mixture of (EtOAc/Hexane: 2/8) to afford an oily product of **3** as a oily liquid (1.2 g, 1.6 mmol, 92%); $[\alpha]_D^{24} = +35°$ (*c* = 0.5 g/dL, $CHCl_3$); IR (KBr, cm^{-1}): *v* = 3417; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.31 (10H, *m*, Ph), 3.62 (1H, t, *J* = 6.6 Hz, OCH_2), 2.09 (1H, *t*, *J* = 7.3 Hz, OCH_2), 1.70–1.63 (2H, *m*, CH-OH), 1.54–1.48 (2H, *m*, CH_2-OH& $CHPPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 132.8, 128.6, 62.5, 34.2, 27.9, and 22.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ = −15.69; MS (*m*/*z*): 518 (M^+), 17%; Anal. for $C_{30}H_{32}O_4P_2$. calcd; C, 69.49; H, 6.22. Found: C, 69.56; H, 6.28.

*2.1.2.7. 1,3,4,6-Tetraacetate-2,5-bis-o-diphenylphosphino-D-mannitol (**5**)*. To a solution of bis-phosphine **4** (50 mg, 0.01 mmol) in pyridine (2 .0 ml) was added Ac_2O (0.05 mmol) under an atmosphere of argon. The reaction was then stirred at RT over night, quenched with water (10 ml), extracted with EtOAc (3 × 25 ml), washed with brine, and dried over $MgSO_4$. The solvent was evaporated subsequently the residue was submitted to NMR analysis without any further purification to afford an oily product of **5** (50 mg, 0.0075 mmol, 75%); $[\alpha]_D^{24} = -56°$ (*c* = 1.0 g/*dL*, *$CHCl_3$*); IR (KBr, cm^{-1}): *v* = 1777; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (5H, *m*, Ph), 7.52–7.46 (5H, *m*, Ph), 4.04 (1H, t, *J* = 5.8 Hz, OCH_2), 2.30 (1H, *t*, *J* = 4.4 Hz, OCH_2), 2.06 (3H, *s*, $CHOCOCH_3$), 1.98 (3H, *s*, CH_2OCOCH_3), 1.71–1.60 (2H, *m*, CH—$OCOCH_3$ and $CHPPh_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 171.2, 130.9, 128.8, 128.6, 63.5, 29.7, 29.5, and 20.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 34.38; Anal. for $C_{38}H_{40}O_8P_2$. calcd; C, 66.47; H, 5.87. Found: C, 66.55; H, 5.90.

3. Results and discussion

The chiral ligand **4** was conveniently synthesized from commercially available *D*-mannitol in three steps, as illustrated in Scheme 1. Commercially available *D*-mannitol was converted into 1,3:4,6-di-*O*-benzylidene-*D*-mannitol **1a–d** (Baggett and Stribblehill, 1977), followed by meslaytion of none-protected alcoholic groups affording compound **2a–d** (Al Majid et al., 2010). Reaction of compound **2a–d** with the strong nucleophilic Ph_2PLi, in THF at −20 °C in anhydrous conditions afforded diphosphine ligands **4**. On the other hand, benzylidene acetal groups are widely used as protecting groups of diols because of their easy introduction and their tolerance to a variety of chemical conditions. These acetals provide a



Scheme 1 Synthesis of ligand 4.

selective 4,6-*O*-protection of pyranoses such as glucose, 2-acetamido-2-deoxy-glucose, galactose, mannose, or altrose. Reductive opening of carbohydrate benzylidene acetals, furnishing benzyl ether at either the C4 or C6 hydroxyl group, was extensively investigated in the literature (Alexander et al., 2007; Kaki Venkata Rao Premanand et al., 2010; and Shie et al., 2009). Selective cleavage of benzylidene acetals under oxidative conditions, allowing formation of a benzoate ester at either the C4 or C6 hydroxyl group, is less frequently employed because most known procedures suffer from rather harsh or environmentally unfriendly conditions. Oxidative cleavage of benzylidene acetals of non-saccharidic acetals using tritylfluoroborate ($Ph_3C^+BF_4^-$) (Deslongchamps et al., 1975), pyridinium dichromate/*tert*-butyl hydroperoxide (Chidambaram et al., 1992; Sato et al., 1988; Ziegler and Tung, 1991; Wiegerinck et al., 1996; Hosokawa et al., 1983), $NaBO_3$ (Bhat et al., 1995), $Co(OAc)_2$/*N*-hydroxyphthalimide (Chen and Wang, 2001; Karimi and Rajabi, 2003), 2,2′-bipyridinium chlorochromate/*m*-CPBA (Luzzio and Bobb, 1997), $NaBrO_3/Na_2S_2O_4$ (Adinolfi et al., 1999), $KBrO_3/Na_2S_2O_4$ (Senthilkumar et al., 2007) and more recently $RuCl_3/NaIO_4$ (Ponminor Senthil et al., 2010) has been evaluated and gave varying degrees of regioselectivity. Similarly, many methods have been developed for the selective oxidative cleavage of 4,6-*O*-benzylidene acetals of pyranosides (Binkley et al., 1984). Ozone (Deslongchamps et al., 1975), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Oikaw et al., 1982; and Zhang and Magnusson, 1996), NBS/H_2O (Deslongchamps et al., 1975), $Pd(OAc)_2$ or $CuCl_2$/*t*-BuOOH (Sato et al., 1988), $NaBrO_3/Na_2S_2O_4$ (Adinolfi et al., 1999), $Co(OAc)_2$/N-hydroxyphthalimide (Chen and Wang, 2001), and $KBrO_3/Na_2S_2O_4$ (Senthilkumar et al., 2007) gave in most cases, the benzoyl esters in high yield but with moderate regioselectivity.

As part of our ongoing interest to develop easy new method for the synthesis of new ligands **4** and **9**, one pot unprecedented reductive ring opening of benzilydine ketals has been taken place and afforded compounds **4** and **9.** Thus, the preparation of a range of 1,3-4,6-di-*O*-benzylidene ketals of *D*-mannitol derivatives was easily achieved by reaction of *D*-mannitol with benzaldehyde derivatives, affording the corresponding 1,3-4,6-di-*O*-benzylidene ketals **2(a–d)** as shown in Scheme 1.

In all cases, reductive ring opening of the 1,3-4,6-di-*O*-benzylidene ketal derivatives was performed using a powerful nucleophilic reagent, Ph_2PLi (0.1 M in THF) under extremely anhydrous conditions, and the resulting solution was stirred at –20° for 24 h. The rate of the cleavage explains the possibility of that librating methanesulfonic acid after displacement by Ph_2PLi could cleave the terminal ketals protecting group giving free alcohol. The isolated yields of the 1,3,4,6-tetrahydroxy-2,5-bis-diphenylphosphine-*D*-mannitol derivatives **3** (Scheme 1) were obtained in moderate to high yield (92% was achieved when *p*-methoxy benzaldehyde was used) as shown in entry 3 in Table 1. IR, ^1H, ^{13}C and ^{31}P NMR in addition to MS spectra established unambiguously the desired structure. For example, IR spectrum revealed a characteristic band for C=O at 1777 cm^{-1}, ^1H NMR spectrum showed that the specific benzyl proton (δ 5.46, *s*, PhCH) and mesyl protons (δ 3.17, s, SO_2CH_3) were disappeared.

The ^{31}P NMR spectrum of **3** displayed a *s* at δ –15.67 ppm. It was attributed to the presence of phosphine atom which reflects its pure diastereoselectivity (Fig. 1). For further confirmation that the ring has been cleaved, we have acetylated the free alcoholic groups using acetic anhydride/pyridine as depicted in Scheme 2 afforded compound **5**. The ^1H NMR

Table 1 Isolated yield of **1**, **2** and **4**.

No. of entry		Ar	Yield (%)		
			1	**2**	**4**
1	**a**	C_6H_5	84	97	80
2	**b**	*p*-$CH_3C_6H_4$	79	84	83
3	**c**	*p*-$CH_3OC_6H_4$	86	84	92
4	**d**	2,4-diClC_6H_3	80	95	78
5	**e**	*p*-$NH_2C_6H_4$	–	–	–

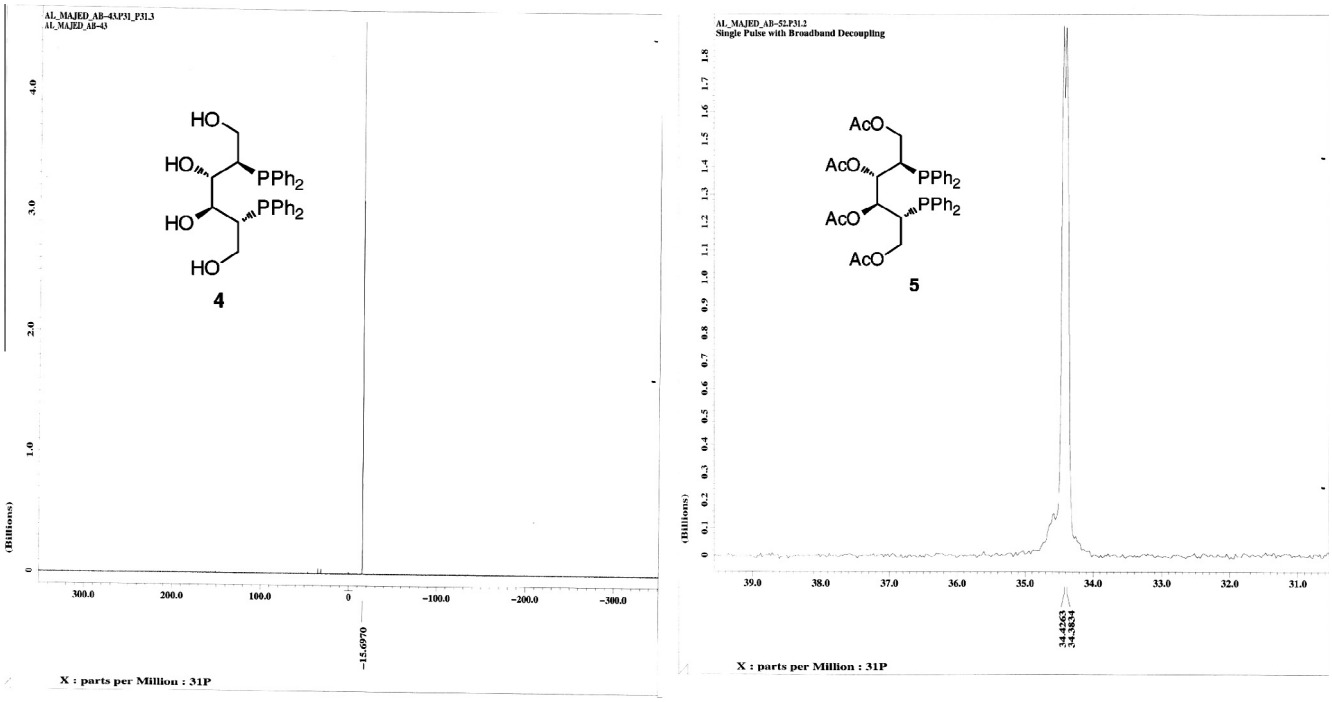
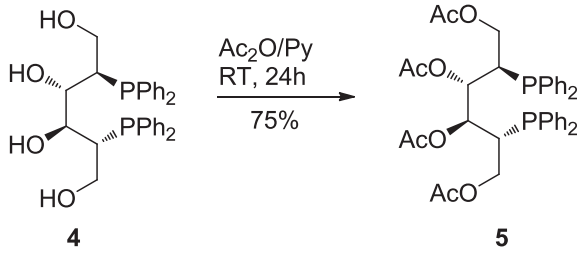


Figure 1 ^{31}P NMR of 4 and 5.

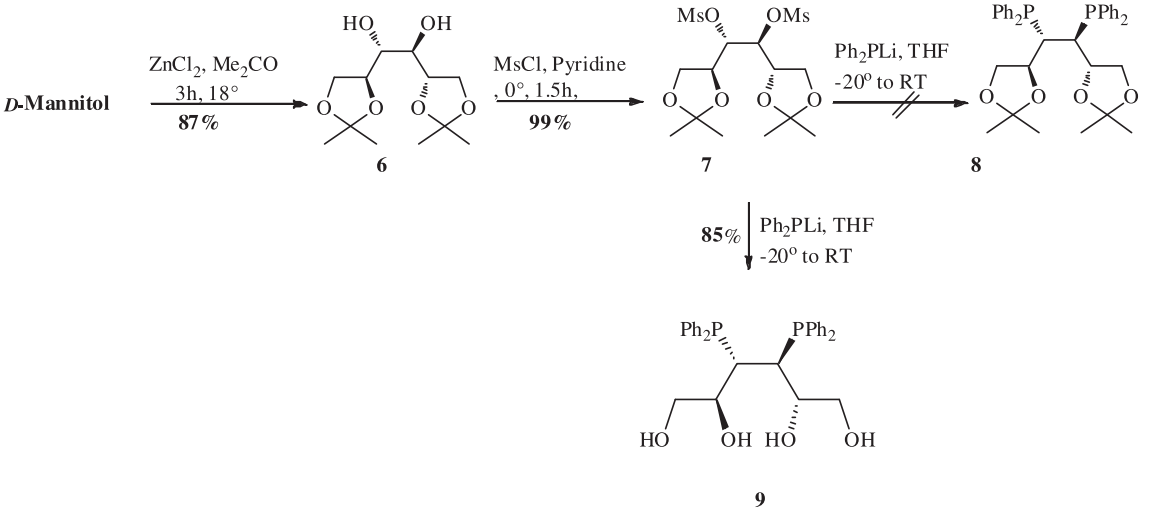


Scheme 2 Synthesis of ligand 5.

spectrum of **5** showed that the specific protons for CH_3CO were appeared at δ 2.06, 1.98 ppm for the 1° and 2° alcoholic groups respectively, and ^{31}P NMR spectrum of **5** displayed a *s* at δ 34.83 ppm (Fig. 1).

As reported in Table 1, synthesis and purification of the corresponding alcohols **1a–d**, bismyslate **2a–d**, and C_2-disphosphine ligand **4** proceeded smoothly except for entry 5 when *Ar* group is bearing the electron rich 4-amino-phenyl substituent: which could not be isolated. In most cases no byproducts were detected and excellent yields were achieved as well. Additionally, excellent diastereoselectivity was confirmed based on ^{31}P NMR which gave singlet peaks.

From these results, the same methodology was applied with different protecting groups instead of benzylidene moieties. Reductive ring cleavage of the bismesylate derivative **7** gave diphosphine ligand **9** in 85% yields as depicted in Scheme 3.



Scheme 3 Synthesis of ligand 9.

The preparation of diphosphine ligands containing benzylidene and ketal moieties **3**, **8** respectively could not be achieved under the same conditions. It was attributed-as we stated early- to unprecedented opening of both rings by the leaving mesylate which probably acts as a strong nucleophilic anion. This of course, led to opening of both benzylidene and ketal rings.

4. Conclusion

On the basis of the experimental results, the following conclusions can be drawn. We have shown that using Ph_2PLi/THF generated a new C_2 diphosphine ligand and reductive ring opening of the 1,3-4,6-*O*-benzylidene ketals. Further chemistry about the new ligand will be investigated in the nearest future.

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